Cefepime-Induced Neurotoxicity: A Case Report

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Background

Cefepime is a broad-spectrum fourth-generation cephalosporin with activity against gram-positive and gram-negative pathogens. It is administered through the intravenous route with an average volume of distribution of 0.2L/kg in healthy adults with normal renal function. It mainly undergoes renal elimination with 85% of the drug being excreted in an unchanged form. This explains the toxicity and its manifestations in patients with pre-existing impaired renal function and those who have acute renal dysfunction in the setting of critical illness/sepsis [7]. The proposed mechanism of cefepime-induced neurotoxicity is mainly mediated by postsynaptic inhibition at the gamma-aminobutyric acid (GABA)(A)-receptors [11]. Symptoms such as depressed consciousness, aphasia, myoclonus, seizures, coma, and death may manifest with decreased levels of elimination or increased central nervous system (CNS) penetration [10]. Close monitoring of the patient's renal function with adequate renal dosing can mitigate any adverse consequences.

Objective

Due to the widespread use of cefepime and the increased prevalence of renal impairment in critically ill patients, this case highlights the importance of understanding the risks when initiating cefepime treatment and practicing close observation of the drug.

Case Presentation

61-year-old male with a past medical history of coronary artery disease, heart failure with reduced ejection fraction, atrial fibrillation, and chronic obstructive pulmonary disease (COPD) and, asbestosis was admitted to the hospital for refractory atrial fibrillation and recurrent ventricular tachycardia with exacerbation of heart failure.

The patient had an initial 6-day intensive care unit (ICU) admission for hypotension requiring vasopressor support and high risk of converting back into ventricular tachycardia. Once hemodynamically stable, he was transferred to the hospitalist teaching service. Upon comparison to chest X-rays taken at the time of transfer to those at admission along with the patient's clinical symptoms, the patient was diagnosed with hospital-acquired pneumonia and subsequently was given Vancomycin 1750mg Q24H IV and Cefepime 1g Q6H IV for broad-spectrum coverage.

On day two of his IV cefepime treatment, the patient developed altered mental status. He was no longer oriented, refusing medications, exhibiting nonsensical language, with writhing/itching of the upper extremities. Vital signs were stable. Neurological examination was negative for any focal deficits. Lab workup (table 1) and noncontract head CT were unremarkable (figure 1).

Upon review of medications and ruling out other etiologies, cefepime-induced neurotoxicity was proposed as the potential cause of the patient's altered mental status and the medication was discontinued in favor of piperacillin-tazobactam. Over the next three days, the patient's mental status improved remarkably.

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Diagnostics and Lab Work

Test	Patient Value	Reference Range
Sodium	128	137-145 mmol/L
Potassium	3.5	3.5-5.1 mmol
Chloride	93	96-107 mmol/L
Carbon Dioxide	27	22-32 mmol/L
Anion Gap	8	3-11 mEq/L
BUN	47	7-20 mg/dL
Creatinine	1.30	0.7-1.5 mg/dL
Est GFR	63	≥60
BUN/Creatinine Ratio	36	10-20
Glucose	83	74-106 mg/dL
Calcium	8.6	8.4-10.2 mg/dL
Phosphorus	2.8	2.5-4.5 mg/dL
Magnesium	2.3	1.6-2.3 mg/dL
Total Bilirubin	3.6	0.1-1.1 mg/dL
AST	289	15-46 Units/L
ALT	680	13-69 Units
Alkaline Phosphatase	178	38-126 Units/L
Total Protein	6.1	6.3-8.2 gm/dL
Urine Nitrite	Negative	Negative
Urine Leuk Esterase	Negative	Negative

TABLE 1: Patient's biochemical and urinalysis results from the day of his altered mental status

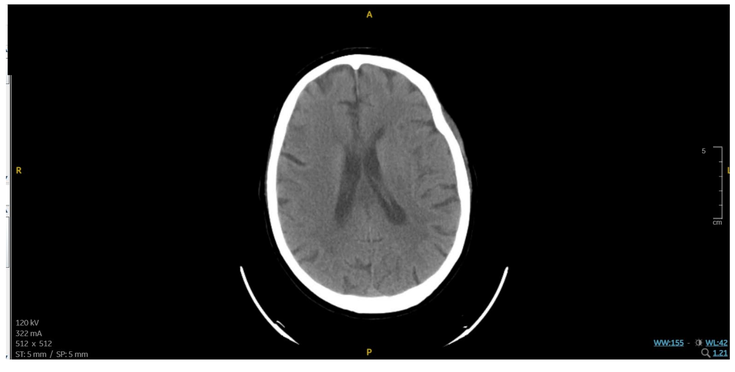

FIGURE 1: Head CT day from the day patient started showing signs of altered mental status

Discussion

- Cefepime is a common antibiotic; however, due to its pharmacokinetics, patients can be at an increased risk of neurotoxicity. Symptoms manifest as perplexing changes in mental status, which may present as a decline in consciousness, confusion, or disorientation. The presence of accompanying myoclonus and renal impairment could raise suspicion for the diagnosis [5].
- Although cefepime-induced neurotoxicity has been traditionally documented in patients with impaired renal function, there has been an increasing incidence of these neurotoxic effects in patients with normal renal function and those with renally adjusted antibiotic dosages [3,9]. Risk factors for increased neurotoxicity susceptibility include advanced age, renal dysfunction, high doses of cefepime, CNS injury, general co-morbidities, or ICU admission [4]. This patient presented with several risk factors that predisposed him to encephalopathy secondary to cefepime including advanced age, multiple co-morbidities, impaired renal function possibly due to underlying cardiorenal syndrome, and an ICU stay.
- There should be a high clinical suspicion for cefepime-induced neurotoxicity with symptom onset one to ten days following initiation of the medication and symptoms typically resolving within two to seven days after discontinuation, [2] as seen with this patient. In severe cases, hemodialysis can be utilized for rapid removal of the drug [6].
- Despite dose adjustment according to creatinine clearance [1,8], the patient still developed signs and symptoms of cefepime-induced neurotoxicity. The patient's cardiorenal state most likely owed to his decreased GFR resulting in decreased elimination of the drug.

Conclusion

Our case study highlights the importance of recognizing Cefepime-induced neurotoxicity as a significant potential cause for altered mental status in patients with normal renal function who develop neurological symptoms after starting Cefepime. Given the potential for multiorgan involvement, such as suspected cardiorenal syndrome in our 61-year-old patient, it is crucial to consider a wide range of possibilities when initiating medications in these individuals. Even with renally adjusted medication dosages, drugs can still exhibit unexpected adverse effects, emphasizing the need for thorough differential diagnosis in such cases.

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